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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,461	12/04/2003	John D. Shaughnessy	D6485	6235

7590 08/10/2005

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,461	SHAUGHNESSY, JOHN D.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-38* is/are pending in the application.

4a) Of the above claim(s) *26-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

3-0-0

Shaughnessy, J.D.

DETAILED ACTION

Election/Restrictions

The Election filed on June 6, 2005 in response to the Restriction Requirement of May 03/2005 has been entered. Applicant's election of Group IV, claims 15, 16 in part, 17 in part, 88 in part and 19-25, as specifically drawn to a method of determining the risk of developing bone disease in test individual comprising examining a human homologue of Dickkopf-1 (DKK1), where the expression level is determined at the protein level is acknowledged and has been entered.

Applicant's election of Group IV, claims 15, 16 in part, 17 in part, 18 in part and 19-25, with traverse is acknowledged. The traversal is on the grounds that the examination of Group III, as specifically drawn to a method of determining the risk of developing bone disease in a test individual comprising examining a human homologue of Dickkopt-1 (DKK1), wherein the expression level is determined at the nucleic acid level both comprise a common WNT signaling antagonist such as DKK1. Thus, Applicants contend that because the instant invention teaches high levels of DKK1 protein expression in plasma cells from cases that showed high DKK1 gene expression, a search of prior art related to a method of Group IV would also reveal prior art relevant to the method of Group II. Hence, the examination of Groups IV and III together will not pose a serious search burden on the Examiner. These arguments have been carefully considered, but are not found persuasive.

The MPEP provides that restriction between inventions is proper; when inventions can be shown to be either independent or distinct, *see* MPEP 803. In the instant case, the inventions have been shown to be either independent or distinct for the reasons set forth in the prior Office Action (05/03/2005, pages 3-4). As to the question of burden of search, the inventions are classified differently, necessitating different searches of the US Patents. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 15-38 are currently pending.

Claims 26-38 have been withdrawn from consideration as being drawn to non-elected inventions.

Claims 15, 16 in part, 17 in part, 18 in part and 19-25, as specifically drawn to expression level being determined at the protein level are currently under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on June 6, 200 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 16, 17 and 18 are objected to because of the following informalities: In the instant case, claim 16 recites a soluble signaling antagonist such as soluble frizzled related protein 3 (SFRP-3/FRZB) which is a non-elected invention. Claim 17 recites wherein said expression level is determined at the nucleic acid level, which is a non-elected invention. Claim 17 recites wherein said expression level is determined by PCR assays, which is a non-elected invention. Applicants are required to amend the currently pending claims as to recite only the elected subject matter.

Applicants are reminded that no new matter should be introduced by amendment to the specification, see MPEP 35 USC 132.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of compounds referred to as "WNT signaling antagonist". However, the written description in this case only sets forth two species of WNT signaling antagonist, wherein said antagonist is soluble frizzled related protein 3 (SFRP-3/FRZB) or the human homologue of Dickkopf-1 (DKK1).

The specification teaches (page 24, line 18 to page 25, line 6) that specific WNT signaling antagonists of the invention include, but are not limited to, compounds which are expressed in a multiple myeloma patient, wherein the increased expression of the antagonist compared to that in a normal individual indicates that the patient has a potential of developing bone disease. The specification further provides (page 19, lines 13-20) examples of secreted antagonists of WNT such as Frizzled (Fz)-related proteins (FRPs), Cerberus, Wnt inhibitor factory (WIF) and Dickkopf (DKK). However, the written description (specification, page 39) only reasonably conveys two species of WNT signaling antagonists (DKK-1 and FRZP) linked to lytic bone lesions in multiple myeloma patients; and therefore, is not commensurate with any and/or all WNT signaling antagonist. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). Some of the factual considerations that are weighed when determining a written description include the level of skill and knowledge in the art, the disclosure of complete or partial structures, the disclosure of physical and or chemical properties, adequate disclosure of the functional characteristics, the correlation between structure and function, and disclosure of methods of making. In the instant case, the specification (page 39) only adequately describes the complete chemical, structural, and functional properties of two species of WNT signaling antagonists (DKK-1 and FRZP) linked to lytic bone lesions in multiple myeloma patients. The specification does not disclose that any of the other WNT signaling antagonists such as Cerberus and Wnt inhibitor factory (WIF), will be expressed in a multiple myeloma patient with a bone disease. The Office has published a synopsis of written description guidelines (www.uspto.gov/web/menu/written.pdf) with particular emphasis on the claiming of a genus with wide varying species (see pages 7-9, Decision Tree). Thus, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of antagonists that encompass the genus of WNT signaling antagonists, which are expressed in a myeloma patient with a bone disease, nor does it provide a description of structural features that are common to the antagonists. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of two species of WNT signaling antagonist is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of antagonists, and therefore conception is not achieved until reduction to

practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only two species of WNT signaling antagonists (DKK-1 and FRZP), wherein the WNT antagonist are linked to lytic bone lesions in multiple myeloma patients, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 15-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method of determining the risk of developing bone disease in a test individual comprising examining the expression level of a WNT signaling antagonist, wherein increased expression of the antagonist compared to that in a normal individual indicates that said test individual has the risk of developing bone disease. Claims must be interpreted as broadly as their terms reasonably allow. Thus, the claims read on a method of determining the risk of a bone disease, which encompasses bone diseases that have yet to form in the mammal.

However, the instant claims are not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to determining the risk of developing any and/or all bone disease in a test individual comprising examining the expression level of a WNT signaling antagonist, wherein increased expression of the antagonist compared to that in a normal individual indicates that said test individual has the risk of developing bone disease. The specification teaches that 174 patients with "newly" diagnosed multiple myeloma, 16 patients with monoclonal gammopathy of undetermined significance, 9 with Waldenstroms macroglobulinemia, and 45 normal persons were studied in the present invention (page 27, lines 10-16). The specification further provides (page 35, Example 8) an analysis of the results obtained from 173 patients with myeloma, wherein the DKK1 signal for patients with 1 + MRI and no x-ray lesion differ significantly compared to patients with no MRI and no x-ray lesions, but does not differ significantly compared to patients with 1 + MRI and 1 + x-ray. Moreover, the specification teaches (page 9, Example 9) a correlation between global gene expression of DKK-1 and lytic bone lesions in multiple myeloma. Thus, while the specification clearly teaches a diagnosis of bone disease in a multiple myeloma patient comprising comparing the level of DKK-1 expression in an individual with multiple myeloma compared to a "normal" individual, the specification appears to be silent on how to interpret this as a method of determining the risk of developing any and/or all bone disease.

In the instant case, the closest prior art, McCarthy (WO 0052047, 2000), to the claimed invention teaches human dickkopf-related proteins (referred to herein as DKK) and uses thereof, wherein one activity associated with the DKK family of proteins is the modulation, e.g., antagonism,

of the activity of the Wnt family of secreted proteins (page 23, lines 16-18). Specifically, the WO document teaches a method of diagnosing a disease or disorder associated with aberrant expression or activity of DKK (abstract). While McCarthy contemplates determining the risk of developing a disease associated with aberrant expression or activity of a DKK protein (page 96, lines 14-16), there does not appear to be any demonstration that the DKK family of proteins can be used to determine risk.

Those of skill in the art recognize that reasonable guidance with respect to assessing the risk of any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and monitored over some period of time prior to the disposition of cancer. The majority of the initial data may be derived from widespread genetic analysis, cancer clusters, or family histories. For example, Chappuis et al. (Cancer Treat Res. 2002; 107: 29-59) discloses an analysis of risk assessment and the importance of genetic testing in ovarian cancer. Specifically, Chappuis et al. teaches that in ovarian cancer, family history is one of the strongest known risk factors, wherein approximately 5 to 13% of all ovarian cancer cases are caused by the inheritance of cancer predisposing genes with an autosomal pattern of transmission (abstract). In addition to genetic factors, McLaughlin et al. (Tannock, I.F. and Hill, R.P., The Basic Science of Oncology, Chapter 2, (3rd Ed., 1998)) teaches that there are a plethora of environmental factors ar which are also determinants for cancer risk in a population. Some environmental factors disclosed by McLaughlin et al. include exposure to tobacco products, dietary factors, alcohol and occupational exposure (page 16). In the instant case, the specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably determine the risk of the development of a bone disease in an individual. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
6/8/04